Molecular Quantum Similarity of Enantiomers: Substituted Allenes

Sara Janssens,[†] **Greet Boon, and Paul Geerlings***

Free University of Brussels (VUB), Faculteit Wetenschappen, Eenheid Algemene Chemie (ALGC),
Pleinlaan 2, B-1050 Brussels, Belgium

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Molecular quantum similarity is evaluated for enantiomers in the case of molecules possessing a chiral axis, as an extension of previous studies on molecules with a single asymmetric carbon atom. As a case study, the enantiomers of substituted allenes are examined. Next to studying global similarity, using the already existing similarity indices defined by Carbó and Hodgkin−Richards, we evaluate local similarity using our earlier proposed local similarity index based on the Hirshfeld partitioning, to quantify the consequences of Mezey's holographic electron density theorem in chiral systems. Furthermore, the relation between the optical activity and the dissimilarity is studied.

1. Introduction

Similarity is a fundamental concept in diverse areas of molecular science, in particular pharmacology and organic chemistry, where molecules are often classified in terms of their "similarity".[1] When designing new molecules, the assumption can be made that systems with similar structures will exhibit similar chemical properties and biological activity. This reasoning incited the search for indices measuring the similarity between molecular structures. The fast evolution of computational techniques now enables scientists to perform a systematic search of similarity which, when quantified can be used in structure−activity relationships.[2]

In recent years Carbó[3] and Hodgkin and Richards[4] among others presented similarity indices based on the electron density, providing information about the similarity of shape and extent of the electron distribution of the systems considered. These indices can also be used in combination with various other reactivity descriptors such as the molecular electrostatic potential (MEP),[4,5] or the Fukui function $f(\mathbf{r})$, which has been introduced within the context of conceptual density functional theory (DFT)[6,7] as a generalization of Fukui's frontier MO concept.

An interesting application of similarity analysis is the case of enantiomers, receiving not much attention in the literature so far besides the work performed within our own research group.[8−11] Studies on enantiomers contain some simplifications due to the identical connectivities of both molecules. The evaluation of the overall, global similarity between enantiomers allows us to replace the discrete, black−white aspect of chirality by a continuously varying property (for an alternative approach see, for example, the beautiful work by Avnir[12,13]). On the other hand, a local counterpart of the similarity index based on the Hirshfeld partitioning technique[14] has been proposed to quantify Mezey's holographic electron density theorem[15] for chiral systems.

The similarity analysis of enantiomers carried out up to now concentrated on systems with a single asymmetric carbon atom.[8,11] As an extension we opted in the present study to examine enantiomers possessing a chiral axis, namely, substituted allenes, which are chiral structures without asymmetric centers. This study gives us the possibility to quantify Mezey's theorem on sp^2 and sp^1 carbon atoms.

The systems under investigation for their global and local similarities are allenes of the type XHC═C═CX′H with X = F, Cl or Br, in analogy with the earlier examined halomethane CHFClBr by Boon et al.[8] These systems considerably simplify things because they do not show conformational flexibility.

A second aim, next to studying global and local similarity indices by means of the total electron density and density difference, is to compare the computed (dis)similarity with the specific rotation $[\alpha]_D$. Supposing that the optical activity, as quantified in a standardized way by the specific rotation $[\alpha]_D$, is an experimentally accessible quantity for the degree of chirality of a molecule and also assuming that the dissimilarity between enantiomers describes their chirality, one can expect a link between the dissimilarity and the optical activity of enantiomers, as was previously shown by Mezey et al.[16] and Boon et al.,[8] albeit that conformational aspects may hide the effect.[10,11]

As, however, no experimental data for the halogenated allenes are available, a "calibration" curve is constructed on the basis of a series of allenes of the type RR′C═C═CR″R‴ with R, R′, R″, R‴ = H, CH_3, CH_2OH, COOH, Ph, for which a vast amount of experimental data of the molar rotation ϕ were reported.[17]

2. Theoretical Basis and Computational Details

2.1. Similarity Indices. Molecular quantum similarity was introduced by Carbó.[3,18] He constructed a normalized similarity index R_{AB} as

$$R_{AB} = \frac{\int \rho_A(\mathbf{r})\,\rho_B(\mathbf{r})\,d\mathbf{r}}{[(\int {\rho_A}^2(\mathbf{r})\,d\mathbf{r})(\int {\rho_B}^2(\mathbf{r})\,d\mathbf{r})]^{1/2}} = \frac{Z_{AB}}{\sqrt{Z_{AA}Z_{BB}}} \quad (1)$$

involving the overlap integral Z_{AB} between the electron densities $\rho(\mathbf{r})$ of molecules A and B, and the self-similarities Z_{AA} and Z_{BB}. Introducing the shape function $\sigma(\mathbf{r})$ defined as the density per particle[19]

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* Corresponding author. Tel: +32 2 6293314. Fax: +32 2 6293317. E-mail: pgeerlin@vub.ac.be.
[†] E-mail address: sajansse@vub.ac.be.

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$$\sigma(\mathbf{r}) = \frac{\rho(\mathbf{r})}{N} \qquad (2)$$

it is easily seen that R_{AB} depends only on the shape function, in line with recent work in the literature on the fundamental nature of this function as a carrier of information.[20−22]

To eliminate the dominant effect of the core electrons in the overlap integral, one can use the density differences $\Delta\rho(\mathbf{r})$[8] instead of the global densities $\rho(\mathbf{r})$ of the two molecules under consideration.

As a consequence of Mezey's holographic electron density theorem,[15] molecular regions (for example, atomic regions around chiral or nonchiral atoms) should contain all the information about the system, thus also about its chirality. In this work we put numerical testing of the consequences of this theorem into practice by concentrating on atomic regions using the Hirshfeld partitioning of the density in atomic contributions $\rho_A(\mathbf{r})$.[14]

This way we can convert the global Carbó index (**1**) into a local analogue, as proposed earlier by Boon et al. in ref 8. For atom C of the *R* and *S* enantiomers of a chiral molecule we propose

$$R_{RS}^{\mathrm{local,C}} = \frac{\int w_{C,R+S}\rho_R(\mathbf{r})\,\rho_S(\mathbf{r})\,d\mathbf{r}}{\{\int w_{C,R}\rho_R(\mathbf{r})\,\rho_R(\mathbf{r})\,d\mathbf{r}\}^{1/2}\{\int w_{C,S}\rho_S(\mathbf{r})\,\rho_S(\mathbf{r})\,d\mathbf{r}\}^{1/2}} = \frac{\int\left(\frac{\rho^0_{C,R}(\mathbf{r}) + \rho^0_{C,S}(\mathbf{r})}{\sum_X \rho^0_{X,R}(\mathbf{r}) + \sum_Y \rho^0_{Y,S}(\mathbf{r})}\right)\rho_R(\mathbf{r})\,\rho_S(\mathbf{r})\,d\mathbf{r}}{\left\{\int\left(\frac{\rho^0_{C,R}(\mathbf{r})}{\sum_X \rho^0_{X,R}(\mathbf{r})}\right)\rho_R(\mathbf{r})\,\rho_R(\mathbf{r})\,d\mathbf{r}\right\}^{1/2}\left\{\int\left(\frac{\rho^0_{C,S}(\mathbf{r})}{\sum_Y \rho^0_{Y,S}(\mathbf{r})}\right)\rho_S(\mathbf{r})\,\rho_S(\mathbf{r})\,d\mathbf{r}\right\}^{1/2}} \qquad (3)$$

where $w_C(\mathbf{r})$ is a weight factor constructed on the basis of the promolecular density $\sum_X \rho^0_X(\mathbf{r})$ and

$$w_{C,R+S}(\mathbf{r}) = \frac{\rho^0_{C,R}(\mathbf{r}) + \rho^0_{C,S}(\mathbf{r})}{\sum_X \rho^0_{X,R}(\mathbf{r}) + \sum_Y \rho^0_{Y,S}(\mathbf{r})}$$

is the weight factor for the total promolecular density $\sum_X \rho^0_{X,R}(\mathbf{r}) + \sum_Y \rho^0_{Y,S}(\mathbf{r})$ of the two enantiomers with their centers C superimposed.[11]

2.2. Relative Orientation of the Enantiomers. An important drawback of the Carbó and Hodgkin−Richards indices is their dependence on the relative orientation of the molecules under consideration. Several methods have already been proposed to establish a criterion on how molecules might be superposed,[11] such as aligning the molecules according to common physicochemical features, or the so-called topo-geometrical superposition algorithm (TGSA) alignment of the molecules based on topological and geometrical features.[23] Another method, the quantum similarity superposition algorithm (QSSA), opts to align the molecules in such a way that the resulting molecular similarity measure is maximized.[24−28]

In this work, we superimpose the backbone of both enantiomers under consideration. This methodology enables us, as opposed to the usage of for example TGSA and QSSA, to evaluate next to the global similarity also the local similarity using the local similarity index (eq 3), not only at the (nonasymmetric) backbone carbon atoms but in some superpositions also on two (nonasymmetric) substituents, to investigate in a quantitative way the holographic electron density theorem.

2.3. Computational Details. In this work, we used a highly efficient analytical implementation of the time-consuming three-dimensional integrations, namely, the BRABO program package developed by Van Alsenoy et al.,[29,30] which allows calculating similarity integrals at a negligible computational cost. The local Carbó index based on the Hirshfeld partitioning (eq 3) is implemented numerically in the program STOCK, part of this BRABO package.[29,30]

All electron densities used in this work were calculated in a DFT approach using the GAUSSIAN 03[31] program at the B3LYP/6-31G* level[32,33] with the constraint of keeping the angle C1−C2−C3 fixed at 180°, whereas calculations of the optical rotation were performed next to this level also with the 6-311++G[34] basis set, which proved to be highly reliable for this purpose.[35]

The conformers of the enantiomers of the $RR'C{=}C{=}CR''R'''$ series were obtained using Spartan[36] and the Merck Molecular Modeling Force Field (MMFF).[37] The lowest energy conformation of each enantiomer has been used.[10]

Optical rotations have been calculated using ab initio density functional theory with gauge-invariant atomic orbitals (GIAOs).[35]

3. Results and Discussion

We distinguish different types of similarities, namely, global and local similarity indices using the total density or the density difference, which we discuss in the following section.

3.1. Global Similarity. In Table 1 we show similarity indices for dihalogen allenes. We rotate the *R* enantiomer around the backbone axis while leaving the *S* enantiomer at its position. The rotations at 0° and 180° give the largest similarity values, both orientations having the backbone carbon atoms and two substituents coinciding.

When the values between Table 1A and Table 1B for global similarities using total densities and density differences are compared, the latter densities mostly yield higher values of similarity. We can say that using density differences is more stringent and sensitive, as these highlight more the chemically important valence regions of the molecules by eliminating the dominant effect of the core electrons. This fact that density differences give different and complementary information about the similarity of the systems confirms the results in ref 8. We notice that this elimination is not very efficient in the case of heavy halogens, whereas for the carbon atom this elimination was sufficient. In the work of Boon et al.[8] for the halomethane CHFClBr we can also see that values for the bromine atom calculated with the total density do not differ much from values calculated with the density difference.

The values of the global similarities in Table 1A and Table 1B differ strongly from 1. Earlier work on the halomethane[8] showed us that the global similarity is larger when heavier atoms coincide in the backbone alignment. In other words, the largest global similarity was found for the orientation where the asymmetric carbon atom and the substituents bromine and chlorine coincide, indicating that in the global similarity index the extent of the electron distribution of the substituents is dominant.

We observe for the symmetrically substituted or "diagonal" dihalogen allenes (dihalogen allenes with two identical halogen substituents, so FF, ClCl and BrBr) the lowest global similarity

TABLE 1: Similarity Index for Dihalogen Allenes (FF, ClCl, BrBr, FCl, FBr, ClBr) at Rotations of 0° and 180° of the *R* versus *S* Enantiomers

A, A′, B. Global Similarity Indices Using the Total Density (A), Using Average Values of Both Rotations (A′) and Using the Density Difference (B)

allene	rotation angle (deg)	A	A′	B
FF	0	0.6265	0.6359	0.6460
	180	0.6452		0.6487
ClCl	0	0.4740	0.4978	0.7787
	180	0.5216		0.7836
BrBr	0	0.4236	0.4616	0.4050
	180	0.4996		0.5130
FCl	0	0.1710	0.5367	0.8139
	180	0.9023		0.5912
FBr	0	0.0194	0.4958	0.1090
	180	0.9722		0.9198
ClBr	0	0.0883	0.4936	0.0901
	180	0.8988		0.9498

C. Local Similarity Indices Using the Total Density[a]

allene	rotation angle (deg)	C1	C2	C3
FF	0	0.9963	0.9999	1.0000
	180	1.0000	0.9999	0.9963
ClCl	0	0.9982	1.0000	1.0000
	180	1.0000	1.0000	0.9982
BrBr	0	0.9976	1.0000	1.0000
	180	1.0000	1.0000	0.9976
FCl	0	0.9982	1.0000	1.0000
	180	1.0000	0.9999	0.9963
FBr	0	0.9977	1.0000	1.0000
	180	1.0000	0.9999	0.9963
ClBr	0	0.9976	1.0000	1.0000
	180	1.0000	1.0000	0.9982

D. Local Similarity Indices Using the Density Difference[a]

allene	rotation angle (deg)	C1	C2	C3
FF	0	0.6631	0.9910	0.9997
	180	0.9996	0.9910	0.6631
ClCl	0	0.7432	0.9937	0.9997
	180	0.9997	0.9937	0.7431
BrBr	0	0.7332	0.9941	0.9997
	180	0.9997	0.9941	0.7331
FCl	0	0.7370	0.9936	0.9996
	180	0.9996	0.9907	0.6633
FBr	0	0.7269	0.9939	0.9996
	180	0.9996	0.9907	0.6621
ClBr	0	0.7338	0.9941	0.9997
	180	0.9997	0.9937	0.7427

E. Local Similarity Indices Using the Total Density with the Extra Constraint[a]

allene	rotation angle (deg)	C1	C2	C3		H	halogen
FF	0	0.9963	0.9999	1.0000	H4 and F5	1.0000	1.0000
	180	1.0000	0.9999	0.9963	H6 and F7	1.0000	1.0000
ClCl	0	0.9982	1.0000	1.0000	H4 and Cl5	1.0000	1.0000
	180	1.0000	1.0000	0.9982	H6 and Cl7	1.0000	1.0000
BrBr	0	0.9976	1.0000	1.0000	H4 and Br5	1.0000	1.0000
	180	1.0000	1.0000	0.9982	H6 and Br7	1.0000	1.0000
FCl	0	0.9982	1.0000	1.0000	H4 and F5	1.0000	1.0000
	180	1.0000	0.9999	0.9963	H6 and Cl7	1.0000	1.0000
FBr	0	0.9977	1.0000	1.0000	H4 and F5	1.0000	1.0000
	180	1.0000	0.9999	0.9963	H6 and Br7	1.0000	1.0000
ClBr	0	0.9976	1.0000	1.0000	H4 and Cl5	1.0000	1.0000
	180	1.0000	1.0000	0.9982	H6 and Br7	1.0000	1.0000

F. Local Similarity Indices Using the Density Difference with the Extra Constraint[a]

allene	rotation angle (deg)	C1	C2	C3		H	halogen
FF	0	0.6625	0.9911	0.9997	H4 and F5	1.0000	1.0000
	180	0.9997	0.9911	0.6625	H6 and F7	1.0000	1.0000
ClCl	0	0.7435	0.9937	0.9997	H4 and Cl5	1.0000	1.0000
	180	0.9997	0.9937	0.7435	H6 and Cl7	1.0000	1.0000
BrBr	0	0.7340	0.9941	0.9997	H4 and Br5	1.0000	1.0000
	180	0.9997	0.9937	0.7435	H6 and Br7	1.0000	1.0000
FCl	0	0.7370	0.9937	0.9997	H4 and F5	1.0000	1.0000
	180	0.9997	0.9908	0.6635	H6 and Cl7	1.0000	1.0000
FBr	0	0.7273	0.9939	0.9997	H4 and F5	1.0000	1.0000
	180	0.9997	0.9907	0.6622	H6 and Br7	1.0000	1.0000
ClBr	0	0.7337	0.9941	0.9997	H4 and Cl5	1.0000	1.0000
	180	0.9997	0.9937	0.7427	H6 and Br7	1.0000	1.0000

[a] Coinciding atoms of *R* and *S* enantiomers are mentioned (backbone carbon, hydrogen, halogen atoms).

value for dibromoallene, and the highest value for difluorallene, because in our case we have two heavy atoms coinciding and at the same time two heavy atoms at a large distance from each other, which obviously is of predominant importance in the global similarity index values.

The global similarities of "nondiagonal" dihalogen allenes (dihalogen allenes with two different halogen substituents: FCl, FBr and ClBr) show this effect even more clearly. Here the couples of coinciding atoms differ from the atoms at large distance from each other. In Table 1A we see that the values at rotation of 180°, when the hydrogen and the heaviest halogen of both enantiomers coincide, is every time larger than the values at 0°, with coinciding atoms the hydrogen and the lightest halogen of both enantiomers. It is as if the heavy halogens, when at a large distance from each other, tear the value of the global similarity down, whereas when the lighter atoms are at a large distance from each other, their effect is negligible in comparison with the then coinciding heavy atoms.

In that respect, the "diagonal" dihalogen allenes show intermediate values, which are almost equal for rotations of 0° and 180°, because these values are not torn down by heavy atoms at large distances from each other, but they have the same halogen at large distances and coinciding. So the effect of the heavy atoms cancels out for "diagonal" dihalogen allenes.

To reduce the impact of the heavy atoms for the "nondiagonal" dihalogen allenes, the average value of the rotations of 0° and 180° is considered in what follows (Table 1A′).

The following sequence is found for the similarity indices:

$$\mathrm{BrBr} < \mathrm{ClBr} \cong \mathrm{FBr} < \mathrm{ClCl} < \mathrm{FCl} < \mathrm{FF}$$

which follows the sequence of the "size" of the atoms and corresponds to chemical intuition.

Note that these are the most similar orientations (rotations at every 30° were calculated for comparison, but all other similarities were smaller), with each time the backbone and two substituents coinciding.

Note that the values at rotations of 0° and 180° for the "diagonal" allenes in Table 1A and Table 1B differ slightly, which is due to a not fully perfect sp^2 character of the carbon atoms C1 and C3.

3.2. Local Similarity. In Table 1C and Table 1D the results for local similarities are given, considering first the three backbone carbon atoms.

Because of the not fully perfect sp^2 character the substituents never coincide, as a result of which we are not able to calculate local similarities for these substituents. A solution for this problem was to work with an extra constraint, namely, a perfect sp^2 character of C1 and C3, the results of which are seen in Table 1E and Table 1F. As expected, we note that the similarity values with this extra constraint are bigger than the values in Table 1C and Table 1D.

At first glance the local similarity indices with the total electron density in Table 1E almost do not differ from unity for the carbon atoms and are even always equal to one within the precision considered (four digits) for the coinciding substituents. The deviation we find for C1 at a rotation of 0° and for C3 at rotation of 180° are not really a consequence of Mezey's holographic electron density theorem, but more an illustration of the fact that the substituents are at large distances from each other at these alignments. So we only find a small deviation quantifying the consequences of Mezey's theorem for some values of the middle carbon atom C2, stating that each region of a molecule contains the information about the whole system, in this case about the chirality. The reason for these only small deviations is due to the contribution of the core electrons when using the total electron density.

When looking at the local similarities with the density difference in Table 1F, we still see substituent values of one, but we find a more significant deviation from one for the carbon atoms. The deviations for C1 at a rotation of 180°, for C3 at a rotation of 0° and for C2 (coinciding atoms with their substituents also coinciding) are for the first time numerical illustrations of Mezey's theorem for sp^2 and sp^1 hybridized carbon atoms, an extension of earlier work within our group for sp^3 carbon atoms.[8,11] Comparing these values, we remark that similarity values for the carbon atoms decrease from sp^3 via sp^2 to sp^1. The density difference is more sensitive for changes in the valence region as reflected in these values as compared to those values in Table 1E using the total electron density.

Note that the deviations from unity are small compared to those noticed in the sp^3 case, e.g., in ref 8, or in other words the consequences of Mezey's holographic theorem are less pronounced, which could be attributed to the less direct chirality source, namely, a chiral axis instead of one or more asymmetric carbon atoms.

The values of C1 at 0° and C3 at 180°, the smallest values, in Table 1C and Table 1E are almost always equal for "diagonal" dihalogen allenes, because the coinciding substituents are equal to the substituents at large distances from each other, so both carbon atoms have equal environments. When looking at these values for "nondiagonal" dihalogen allenes, we notice a larger difference between both values, due to a different environment because of different substituents coinciding or at large distances from each other on both atoms.

We find the same trend, but more pronounced, in Table 1D and Table 1F for local similarity indices with the density difference.

Comparing Table 1A and Table 1B with Table 1C/E and Table 1D/F shows a larger variation for the global indices with rotation of an enantiomer, indicating that global and local indices contain different information.

3.3. Relation between Dissimilarity and Optical Rotation. Supposing that the optical rotation, as quantified by the specific rotation $[\alpha]_D$, is an experimentally accessible quantity for the degree of chirality of a molecule and also assuming that the dissimilarity between enantiomers describes their chirality, one can expect a link between the dissimilarity and the optical rotation of enantiomers, as was previously shown by Mezey et al.[16]

As mentioned in the Introduction experimental data of the molar rotation ϕ are available for allenes of the type $RR'C{=}C{=}CR''R'''$.[17] The relation between the molar rotation ϕ and the specific rotation $[\alpha]_D$ is

$$\phi = [\alpha]_D \frac{M}{100} \qquad (4)$$

and the specific rotation $[\alpha]_D$ can be converted to the optical rotation α by[38]

$$\alpha = [\alpha]_D c l \qquad (5)$$

where M is the molar mass of the optical active substance, c is the concentration and l is the distance of a monochromatic light of wavelength λ.

These experimental data enable us to compare our theoretically calculated values of the molar rotation with the experimental measured values, from which we can establish a "calibration curve" (Figure 1). We calculated the theoretical values in different ways to investigate the influence of basis set (the smaller basis used for the similarity analysis and the

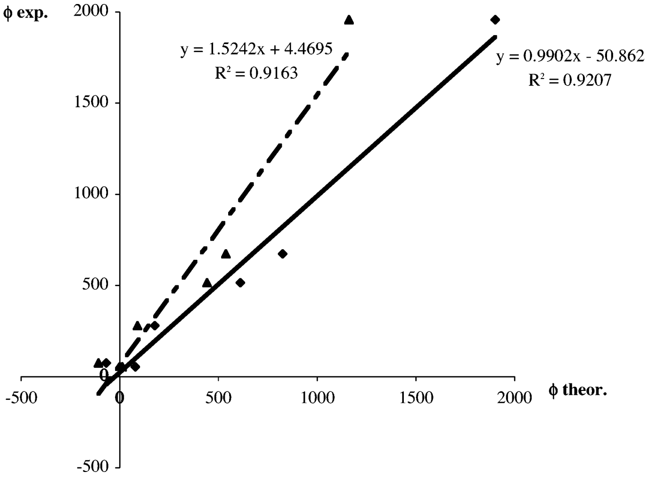

Figure 1. “Calibration curve”: comparison of experimental values of the molar rotation ϕ with theoretical values, calculated in two different ways (small basis set 6-31G* without solvent effect (—) and large basis set 6-311++G(2d,2p) with solvent effect (---)).

larger one previously recommended[35]) and solvent (in the case of the larger basis). In the PCM procedure the same solvent was used as in the corresponding experimental data.

From the R^2 values (the determination coefficient) we can see that the approach with the solvent effect shows good results. The case without solvent effect shows a similar correlation coefficient, the slope being even better. The overall results allow us to conclude that our theoretical calculated values of ϕ are reliable.

Proceeding with our own simpler systems, the dihalogen allenes XHC=C=CX′H, we see that the values for the optical rotation $[\alpha]_D$ (Table 2) decrease with increasing size of the basis, as was the case in the “calibration curve” (Figure 1).

When comparing these values with calculated values of nonsubstituted allenes in function of the dihedral angle,[39] we find the same order of magnitude, that is, values within the range 100−1000.

We also calculated the optical rotation with the extra constraint of keeping the C1 and C3 carbon atoms strictly sp^2 hybridized in Table 3. We see that these values are smaller than the values without this extra constraint, but the order of magnitude is equal.

TABLE 2: Influence of the Basis Set on the B3LYP Calculated Optical Rotation [α] of the *S* Enantiomer for Dihalogen Allenes in the Gas Phase[a]

allene	6-31G*	6-311++G (2d, 2p)
FF	−1	−46
ClCl	501	363
BrBr	523	408
FCl	115	65
FBr	117	74
ClBr	492	369

[a] 6-31G* vs 6-311++G(2d,2p) results are shown.

TABLE 3: Calculated Optical Rotation [α] of the *S* Enantiomer for Dihalogen Allenes in the Gas Phase with the Extra Constraint of Perfect sp^2 Hybridized C1 and C3 Atoms for Both the Small and Large Basis Sets at the B3LYP Level

allene	6-31G*	6-311++G (2d, 2p)
FF	−9	−56
ClCl	494	358
BrBr	517	403
FCl	106	56
FBr	110	66
ClBr	489	366

Anyway, the calculations with and without the extra constraints give the same sequence, and also both basis sets give almost the same sequence for the optical rotation, namely

$$\mathrm{BrBr} > \mathrm{ClBr} \cong \mathrm{ClCl} > \mathrm{FBr} \cong \mathrm{FCl} > \mathrm{FF}$$

where the values for ClBr and ClCl reverse in both basis sets but are quite close to each other. This sequence corresponds with the sequence of the size of the substituent atoms, which means that as the substituents get larger, the optical rotation increases and the enantiomers become more dissimilar (and so less similar). This result is in line with the results by Mezey[15] and our group in the case of the simplest amino acids,[8] although the exact nature of the correlation is not known. In the case of amino acids showing more conformational freedom, less clear-cut trends were found.[11]

As mentioned in paragraph 3.1., we use the average values of the global similarity index so that the impact of the heavy atoms on the symmetry is minimized (Table 1A′).

Comparing these average values of the global similarity index with the optical rotation $[\alpha]_D$, we find following sequences:

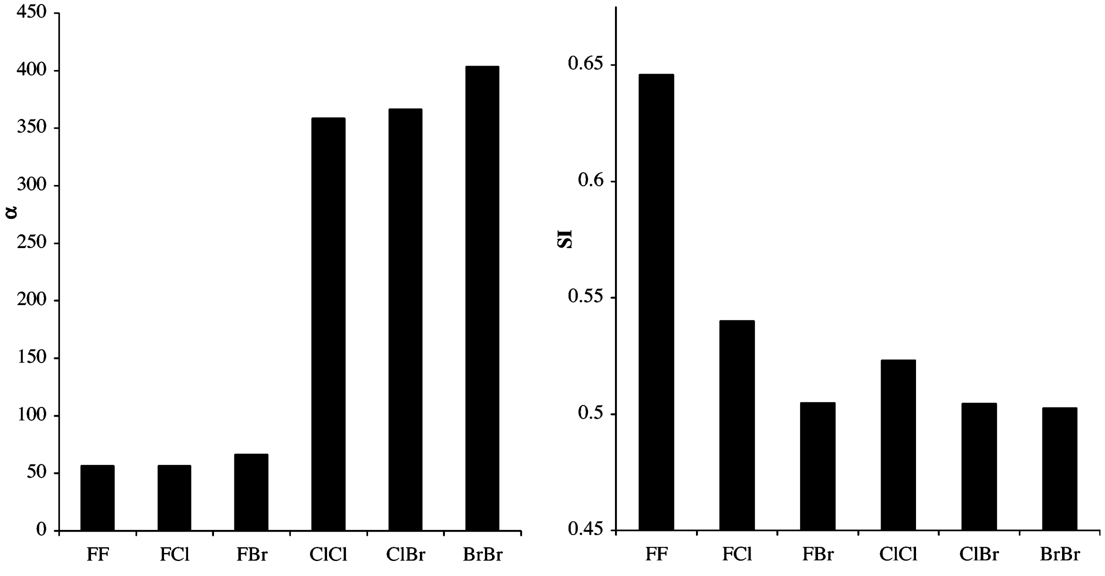

Figure 2. Optical rotation, calculated with large basis set 6-311++G(2d,2p), compared with the average values of the global similarity index, both with the C1 and C3 carbon atoms strictly sp^2 hybridized. (Left): Optical rotation α. (Right): Global similarity index SI.

$$\text{SI:}\quad \text{BrBr} < \text{ClBr} \cong \text{FBr} < \text{ClCl} < \text{FCl} < \text{FF}$$

$$[\alpha]_D:\quad \text{BrBr} > \text{ClBr} \cong \text{ClCl} > \text{FBr} \cong \text{FCl} > \text{FF}$$

which is in nice agreement with the expectations, namely, that a high value of the global similarity yields a low value of the optical rotation, the situation being parallel with the case of chiral systems with one asymmetric center without much conformational freedom.

Both sequences are plotted versus the studied molecules in Figure 2 (with the extra constraint and for the large basis set) yielding a “mirror” image pattern reflecting the trends mentioned above.

4. Conclusions

In this work we provided a contribution to the study of molecular similarities. These were calculated for enantiomers without chiral centers, namely, substituted allenes.

The global similarity was studied using the Carbó and Hodgkin and Richards similarity indices, whereas the local similarity was evaluated with the local similarity index based on the Hirshfeld partitioning presented by Boon.[8]

The results for substituted allenes $XHC{=}C{=}CX'H$ with X, $X' =$ F, Cl or Br, show the complementary information obtained by studying global and local (dis)similarity using both the total electron density and the density difference.

The global dissimilarity turns out to be strongly influenced by the positioning of the atoms at large distances from each other.

The local approach of studying similarity, using the local similarity index based on the Hirshfeld partitioning (eq 3), illustrates the Holographic electron density theorem. Local dissimilarity, and thus “local” chirality, shows up even if the atomic regions considered are nonasymmetric.

The optical activity can be considered as an indicator of global chirality of the whole molecule and can be related to the global dissimilarity between pairs of enantiomers. Theoretical values for the molar rotation for the dihalogen allenes were shown to be reliable by comparing experimental and theoretical values available for allenes of the type $RR'C{=}C{=}CR''R'''$.

Proceeding with the dihalogen allenes $XHC{=}C{=}CX'H$, we find that the molar rotation sequence corresponds with the sequence of the size of the substituent atoms. Comparing the average values of the global similarity index with the optical rotation, we find a good agreement with the expectations, namely, that a high value of the global similarity yields a low value of the optical rotation, in line with previous results on simple amino acids (systems containing a single asymmetric center without too much conformational flexibility). The precise nature of the correlation calls for further investigations.

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References and Notes

(1) Rouvray, D. H. In *Concepts and Applications of Molecular Similarity*; Johnson, M. A., Maggiora, G. M., Eds.; Wiley-Interscience: New York, 1990; p 15.

(2) Mishra, P. C.; Kumar, A. In *Molecular Electrostatic Potentials: Concepts and Applications, Theoretical and Computational Chemistry*; Murray, J. S., Sen, K., Eds.; Elsevier: Amsterdam, 1996; Vol. 3.

(3) Carbó, R.; Arnau, M.; Leyda, L. *Int. J. Quantum Chem.* **1980**, *17*, 1185.

(4) Hodgkin, E. E.; Richards, W. G. *Int. J. Quantum Chem.* **1987**, *14*, 105.

(5) Bonaccorsi, R.; Scrocco, E.; Tomasi, J. *J. Chem. Phys.* **1970**, *52*, 5270.

(6) Parr, R. G.; Yang, W. In *Density-Functional Theory of Atoms and Molecules*; Oxford University Press and Clarendon Press: New York and Oxford, U.K., 1989.

(7) Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* **2003**, *103*, 1793.

(8) Boon, G.; Van Alsenoy, C.; De Proft, F.; Bultinck, P.; Geerlings, P. *J. Phys. Chem. A* **2003**, *107*, 11120.

(9) Geerlings, P.; Boon, G.; Van Alsenoy, C.; De Proft, F. *Int. J. Quantum Chem.* **2005**, *101*, 722.

(10) Boon, G.; Van Alsenoy, C.; De Proft, F.; Bultinck, P.; Geerlings, P. *J. Mol. Struct. (THEOCHEM)* **2005**, *727* (R. Carbó Volume), 49.

(11) Boon, G.; Van Alsenoy, C.; De Proft, F.; Bultinck, P.; Geerlings, P. *J. Phys. Chem. A* **2006**, *110*, 5114.

(12) Zabrodsky, H.; Avnir, D. *J. Am. Chem. Soc.* **1995**, *117*, 462.

(13) Alvarez, S.; Alemany, P.; Avnir, D. *Chem. Soc. Rev.* **2005**, *34*, 313 and references therein.

(14) Hirshfeld, F. L. *Theor. Chim. Acta* **1977**, *44*, 129.

(15) Mezey, P. G. *Mol. Phys.* **1999**, *96*, 169.

(16) Mezey, P. G.; Ponec, R.; Amat, L.; Carbó-Dorca, R. *Enantiomer* **1999**, *4*, 371.

(17) Runge, W. In *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1980; Part 1, p 99.

(18) Bultinck, P.; Gironés, X.; Carbó-Dorca, R. *Rev. Comput. Chem.* **2005**, *21*, 127.

(19) Parr, R. G.; Bartolotti, L. J. *J. Phys. Chem.* **1983**, *87*, 2810.

(20) Ayers, P. W. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 1959.

(21) De Proft, F.; Ayers, P. W.; Sen, K. D.; Geerlings, P. *J. Chem. Phys.* **2004**, *120*, 9969.

(22) Geerlings, P.; De Proft, F.; Ayers, P. W. In *Theoretical Aspects of Chemical Reactivity, Theoretical and Computational Chemistry*; Toro Labbé, A., Ed.; Elsevier: Amsterdam; Vol. 16 (in press).

(23) Gironés, X.; Robert, D.; Carbó-Dorca, R. *J. Comput. Chem.* **2001**, *22*, 255.

(24) Bultinck, P.; Kuppens, T.; Gironés, X.; Carbó-Dorca, R. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 1143.

(25) Bultinck, P.; Carbó-Dorca, R.; Van Alsenoy, C. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 1208.

(26) Amat, L.; Carbó-Dorca, R. *Int. J. Quantum Chem.* **2002**, *87*, 59.

(27) Constans, P.; Carbó-Dorca, R. *J. Chem. Inf. Comput. Sc.* **1995**, *35*, 1046.

(28) Constans, P.; Amat, L.; Carbó-Dorca, R. *J. Comput. Chem.* **1997**, *18*, 826.

(29) Rousseau, B.; Peeters, A.; Van Alsenoy, C. *Chem. Phys. Lett.* **2000**, *324*, 189.

(30) Van Alsenoy, C.; Peeters, A. *J. Mol. Struct. (THEOCHEM)* **1993**, *105*, 19.

(31) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision B.03; Gaussian, Inc.: Pittsburgh, PA, 2003.

(32) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(33) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(34) Krishnan, R.; Frisch, M. J.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 4244.

(35) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J.; Mennucci, B.; Tomasi, J. *Tetrahedron: Asymmetry* **2000**, *11*, 2443.

(36) Spartan Dec Version 5.1.3 X11.

(37) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490.

(38) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 1119.

(39) Ruud, K.; Helgaker, T. *Chem. Phys. Lett.* **2002**, *352*, 533.